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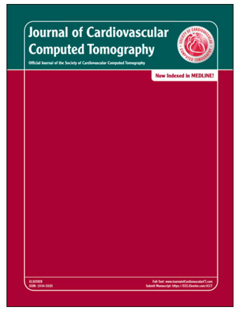

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Rong Bing, Roel S. Driessen, Paul Knaapen, Marc R. Dweck

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Review article

The Clinical Utility of Hybrid Imaging for the Identification of Vulnerable Plaque and Vulnerable Patients

Short title: Hybrid imaging of vulnerable plaque

Rong Bing[1] MBBS, Roel S Driessen[2] MD, Paul Knaapen[2] MD PhD, Marc R Dweck[1] MD PhD

[1] BHF Centre for Cardiovascular Science, University of Edinburgh, 47 Little France Crescent, Edinburgh, United Kingdom

[2] Department of Cardiology, VU University Medical Centre, de Boelelaan 1117 1081 HV Amsterdam, The Netherlands

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Address for correspondence:

Dr Marc R Dweck

BHF Centre for Cardiovascular Science, University of Edinburgh

47 Little France Crescent

Edinburgh EH16 4TJ

Tel: +44 131 242 6515 Email: Marc.dweck@ed.ac.uk Twitter: @MarcDweck

ABSTRACT

Despite decades of research and major innovations in technology, cardiovascular disease remains the leading cause of death globally. Our understanding of major cardiovascular events and their prevention is centred around the atherosclerotic plaque and the processes that ultimately lead to acute plaque rupture. Recent advances in hybrid imaging technology allow the combination of high spatial resolution and anatomical detail with molecular assessments of disease activity. This provides the ability to identify vulnerable plaque characteristics and differentiate active and quiescent disease, with the potential to improve patient risk stratification. Combined positron emission tomography and computed tomography is the prototypical non-invasive hybrid imaging technique for coronary artery plaque assessment. In this review we discuss the current state of play in the field of hybrid coronary atherosclerosis imaging.

KEYWORDS

Vulnerable plaque

Atherosclerosis

Computed tomography coronary angiography

Myocardial perfusion

Positron emission tomography

Fractional flow reserve

Coronary physiology

ABBREVIATIONS

CMR	Cardiac magnetic resonance
CT	Computed tomography
CTCA	Computed tomography coronary angiography
FFR	Fractional flow reserve
FFR_{CT}	Computed tomography coronary angiography-derived fractional flow reserve
MRCA	Magnetic resonance coronary angiography
PET	Positron emission tomography

INTRODUCTION

Cardiovascular disease is the leading cause of death globally, despite advances in risk stratification, diagnostic tools and preventative therapies (1). Consequently, there remains major interest in refining our current methods of diagnosis and risk stratification to better individualise preventative therapies. Myocardial infarction is most commonly caused by rupture of atherosclerotic plaque. Plaques that are prone to rupture have certain common characteristics that together define the vulnerable plaque. Vulnerable plaques have played an integral role in our understanding of atherosclerosis and cardiovascular disease, with extensive research conducted to better characterise and identify these lesions (2). However, appreciation of the fact that the majority of vulnerable plaques ruptures are clinically silent has led to a paradigm shift in atherosclerotic plaque imaging; focus has shifted from the level of the individual plaque to the patient (3), and from invasive to non-invasive imaging modalities. This change has coincided with advances in non-invasive imaging techniques which now facilitate comprehensive assessments of plaque characteristics and disease activity across the coronary vasculature. Hybrid cardiovascular imaging is at the frontier of clinical research in this field, although it has yet to become adopted for routine clinical use.

HYBRID IMAGING: RATIONALE AND CONCEPTS

The pathophysiology of atherosclerosis and the vulnerable plaque is well-described (2). There are hallmarks characteristics of high-risk plaque that have been identified on histology, invasive intracoronary imaging and computed tomography coronary angiography (CTCA) which serve as specific targets for hybrid coronary imaging. The prototypical thin-cap fibroatheroma features inflammation (predominantly macrophage infiltration), a large lipid-rich necrotic core, a thin fibrous cap (<65 μm), superficial microcalcification and plaque haemorrhage. Notably, these findings are independent of stenosis severity; myocardial infarction is often due to plaque rupture in non-obstructive lesions (4, 5). As our ability to image these plaques has improved it has become clear that the majority of these lesions appear to either heal or rupture sub-clinically with only very few leading to myocardial infarction. In the landmark PROSPECT trial (4), 596 thin-cap fibroatheromas were identified on virtual-histology intravascular ultrasound (IVUS) in a cohort of 697 patients with acute coronary syndrome. After 3 years' follow-up, only 31 myocardial infarctions, cardiac arrests or cardiac deaths occurred. Of these, 14 were related to the original culprit lesion. The recent Lipid Rich Plaque study demonstrated that the lipid core burden index on near-infrared spectroscopy IVUS predicted both culprit and non-culprit major adverse cardiovascular events at 24 months (6). The value of invasive assessments of plaque morphology and plaque-directed therapies has therefore been questioned. Vulnerable plaque assessment appears to be of greater value at the level of the patient, using non-invasive imaging to interrogate the entire coronary vasculature. Those subjects in whom adverse plaque characteristics are identified are at increased risk of future events, although the originally identified lesion may not itself result in a clinical event. As such, total atherosclerotic burden has yet to be superceded for prognostic purposes by any plaque-level imaging (3).

Hybrid imaging techniques combine two different modalities, taking advantage of their individual strengths to provide a comprehensive dataset. A modality with high temporal and spatial resolution is required to provide anatomical detail and assessments of soft tissue composition. For the coronary arteries, the most common of these is CTCA, although cardiovascular magnetic resonance (CMR) can also be utilised. For hybrid coronary plaque assessment, this dataset is most commonly fused with positron emission tomography (PET). This allows interrogation of plaque biology and potentially any disease process but requires appropriately targeted radiotracers. The ability of hybrid PET-CT and PET-MR to provide this breadth of information about anatomy, plaque composition and disease activity make them exciting techniques with which to study coronary atherosclerosis.

HYBRID IMAGING: PLAQUE CHARACTERISTICS

Non-invasive imaging of vulnerable plaque morphology has been extensively studied with CT and MR as described below.

Computed tomography coronary angiography

CTCA has been at the forefront of coronary plaque characterisation for many years, with studies demonstrating close correlation between CTCA and intravascular imaging findings of thin-cap fibroatheromas (7, 8). There are several classic CTCA features of vulnerable plaque: low-attenuation (<30 Hounsfield Units), positive remodelling (commonly defined as a remodelling index >1.1), spotty calcification and the napkin-ring sign (low-attenuation plaque core with a rim of higher attenuation). Early data from Motoyama *et al* described the increased prevalence of low attenuation plaque (79% vs 9%), positive remodelling (87% vs 12%) and spotty calcification (63% vs 21%) in culprit lesions compared to stable lesions (9). Further prospective data demonstrated an increased rate of acute coronary syndromes in patients with high-risk plaque (16.3% vs 1.4% at mean follow-up of 3.9 ± 2.4 years, hazard ratio [HR] 8.24 (95% confidence interval [CI] 5.26 – 12.96)) (10). There now exists a large body of non-randomised evidence supporting these findings (5, 9-12). Recent analyses from the two largest randomised trials of CTCA in symptomatic patients with suspected stable coronary artery – the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and Scottish Computed Tomography of the Heart (SCOT-HEART) trials – have added further weight to the prognostic power of CTCA assessments of vulnerable plaque. In PROMISE, 676 (15%) patients had high-risk plaque, conferring a greater risk of major adverse events after adjustment for significant stenoses and atherosclerotic cardiovascular disease risk score (HR 1.72, 95% confidence interval [CI] 1.89 – 3.93) (13). Of note, this incremental prognostic power was seen only in patients with non-obstructive disease. In SCOT-HEART, adverse plaque features, present in 608 (34%) patients (40% of patients with non-obstructive plaque and 75% in those with obstructive plaque), conferred a 3-fold higher risk of coronary heart disease death or nonfatal myocardial infarction (HR 3.01, 95% CI 1.61 – 5.63), an effect that was most pronounced during short-term follow-up. The high prevalence of adverse plaque features demonstrates the relatively low positive predictive value of these findings. The prognostic power of adverse plaque features was not independent of coronary artery calcium score, highlighting the importance of total atherosclerotic disease burden. Additionally, approximately half of patients with subsequent adverse events did not have obstructive coronary artery disease, while (14). It is important to note the clinical context of these trials, as vulnerable plaque features may perhaps be more relevant in the acute setting (15) due to the dynamic nature of plaque biology and the increased use of long-term preventative therapies .

Cardiovascular magnetic resonance

CMR has become an imaging modality of major interest in recent years as a result of improvements in scanner technology and software. CMR offers a multiparametric approach to cardiovascular imaging, providing unparalleled soft tissue characterisation that is of particular value in the myocardium, alongside information regarding anatomy, function, perfusion and viability. CMR is also able to characterise coronary atherosclerosis, utilising non-contrast T1-weighted (black blood) imaging to detect methaemoglobin found in acute intraplaque haemorrhage or intraluminal thrombosis. High-intensity coronary plaques correlate well with CTCA findings of low attenuation and positive remodelling, demonstrate increased rates of in-situ thrombus, and have been shown to reduce in intensity after statin therapy (16-20). Meanwhile, novel targeted contrast agents have been developed, such as THI0567-targeted liposomal-gadolinium. This agent binds with high affinity to integrin α4β1, a key integrin involved in recruiting inflammatory cells to atherosclerotic plaques, and is able to detect vulnerable aortic plaque in an animal model (21). However, as a result of the inferior spatial resolution compared to CTCA, magnetic resonance coronary angiography (MRCA) is largely restricted to the proximal and mid-vessel coronary segments. Sequences such as the Coronary Atherosclerosis T1-weighted Characterization with integrated anatomical reference (CATCH) (22) have been developed to overcome some of these limitations but remain exploratory at this point in time. The majority of clinical research and histological validation has therefore focused on larger, stationary vessels such as the carotid artery. Longer scan times in comparison to CTCA, cost and accessibility are other potential barriers to wider uptake of CMR for imaging of coronary atherosclerosis.

HYBRID IMAGING: DISEASE ACTIVITY

Molecular nuclear imaging techniques utilise targeted probes bound to radioactive isotopes. An understanding of plaque biology and the various components of vulnerable plaque are critical to determine suitable targets for molecular imaging. PET has been studied for many years, primarily in other specialties such as oncology. Coronary PET imaging has previously been limited due to poor spatial resolution, partial volume effects and cardiac motion. However, with improvements in scanners and the development of advanced motion correction and co-registration techniques, many of these limitations have been overcome. There is now major research interest in coronary PET imaging for the assessment of disease activity within atherosclerotic plaques. This interest had led to the advent of bespoke tracers targeting specific aspects of plaque biology to complement the use of more established radiotracers that have been re-purposed from other fields.

Positron emission tomography: 18F-fluorodeoxyglucose

18F-fluorodeoxyglucose (18F-FDG) PET has been used widely in oncology for many years and was first utilised to image atherosclerosis in the carotid artery in 2002 (23). As a glucose analogue, it is metabolised and accumulates intracellularly in tissues with high metabolic activity via the glucose transporter protein system. 18F-FDG has therefore been used as a non-specific marker of vascular inflammation in the aorta, carotids and femoral arteries. 18F-FDG uptake has been shown to correlate with the presence of atherosclerosis, features of plaque vulnerability, biomarkers of inflammation (in particular macrophage burden) and clinical cardiovascular risk (24-26).

Although the 18F-FDG PET is excellent for myocardial viability assessment due to avid uptake in cardiomyocytes, coronary artery uptake is often obscured by the adjacent myocardial signal. This is the main limitation of 18F-FDG for coronary atherosclerosis imaging, even despite dietary restrictions prior to scanning (27-29). 18F-FDG may still prove of value in detecting plaque inflammation in the aorta and carotid arteries; large prospective outcome studies are awaited.

Positron emission tomography: 18F-sodium fluoride

Given 18F-FDG's lack of specificity, other radiotracers have been explored. 18F-sodium fluoride (18F-NaF) has been used as a bone tracer and for the detection of bony metastases for many decades but has now found a potential application in hybrid cardiac imaging. The ligand for 18F-NaF is hydroxyapatite, a key component of early bone and vascular calcification. It preferentially binds to micro- rather than macrocalcification due to the higher exposed surface area of hydroxyapatite (30). Microcalcification is thought to be an early healing response to cell necrosis and inflammation that precedes the development of larger, macroscopic deposits of calcium which can stabilise plaque. Microcalcification within a thin fibrous cap may also increase local stress and destabilize the plaque, thereby increasing the chance of rupture (31). Coronary microcalcification is therefore a key component of vulnerable plaque and a biologically plausible target for imaging, with 18F-NaF providing different information to the more established, stable macrocalcification identified on CT.

18F-NaF PET-CT was noted to identify aortic plaque in 2010 (32). Subsequent data has shown that increased 18F-NaF activity can be identified in the coronary arteries, localising to individual plaques and demonstrating excellent inter-observer repeatability (33). This improved ability to detect discrete coronary artery uptake compared to 18F-FDG appears to be due to low 18F-NaF uptake in the adjacent myocardium and very high affinity of the tracer for microcalcification (30, 34) Again, 18F-NaF appears to be providing different information to the presence of calcium on CT; in one study, almost a half of patients with a calcium score >1000 Agatston units did not have any coronary 18F-NaF uptake (33). In keeping with the hypothesis that 18F-NaF uptake is associated with vulnerable plaque, several clinical studies have demonstrated uptake to be associated with culprit and high-risk coronary plaque as defined by invasive angiography, intravascular ultrasound and CTCA. In the first report, increased 18F-fluoride uptake was observed at the site of the culprit coronary plaque in 37 of the 40 patients with recent myocardial infarction (29), a finding supported by two subsequent smaller studies (35, 36).

Recent technological advances have greatly improved the image quality of coronary 18F-NaF PET-CT imaging. These techniques have focused on optimizing image reconstruction and correcting for cardiac, respiratory and gross patient motion, with the important advantage that they can be applied retrospectively to PET datasets (37-39). Newer data have also demonstrated the feasibility of fusing PET data with previously acquired CTCA, expanding the potential practical application of this form of imaging (40). 18F-NaF PET-MR is also feasible with lower doses of ionising radiation, but currently cannot provide the spatial resolution of CTCA for coronary artery imaging (41).

Positron emission tomography: other radiotracers

Multiple alternative radiotracers, each with a specific target, have been studied for use in atherosclerosis (Table 1) (42). 68Ga-DOTATATE, which targets the somatostatin receptor subtype 2 (SSTR2) on the surface of activated proinflammatory M1 macrophages, has recently been investigated for coronary atherosclerosis imaging. The Vascular Inflammation imaging using Somatostatin receptor positron emissION tomography (VISION) study utilised RNA sequencing, autoradiology, histology and PET-CT in patients with stable and unstable cardiovascular disease. The investigators elegantly demonstrated exclusive expression of SSTR2 in M1 macrophages within atherosclerotic plaque, a strong correlation between SSTR2 expression and 68Ga-DOTATATE activity, and improved discrimination of culprit and high-risk plaque in both the coronary and carotid arteries compared to 18F-FDG (43). Further studies are keenly anticipated. Other examples of alternative radiotracers include 11C-PK11195, which is a specific ligand of the translocator protein that is highly expressed on activated phagocytes, and the chemokine receptor CXCR4, which is upregulated in unstable plaque and colocalizes with CD68 inflammatory cells. 11C-PK11195 is able to image intraplaque haemorrhage in recently symptomatic carotid plaques (44) as well as active disease in large-vessel vasculitis, while CXCR4 has recently shown promise for the distinguising culprit and non-culprit coronary plaques in ST-elevation myocardial infarction (45).

HYBRID IMAGING: PHYSIOLOGY

In addition to measurements of plaque composition and disease activity, PET/CT also allows for functional assessments of atherosclerotic lesions, whether using myocardial perfusion studies or non-invasive fraction flow reserve (FFR). This is of interest as recent data have suggested that vulnerable plaque characteristics are associated with haemodynamically significant lesions, and that integrating luminal stenosis, adverse plaque characteristics and adverse haemodynamic characteristics (comprised of CT-derived FFR (CT-FFR), delta CT-FFR across the vessel, wall shear stress and axial plaque stress) provides better identification of culprit lesions than each individual parameter (46). Functional coronary assessments may therefore act as both surrogates of adverse plaque features, as well as an additional modality to add incremental prognostic information.

With invasive FFR now routinely used for decision making in interventional cardiology, interest has grown in the potential for CT-FFR to enhance the role of CTCA as a gatekeeper to invasive angiography. Although CT-FFR does not image vulnerable plaque directly, several studies have demonstrated that CTCA assessments of plaque composition improve discrimination of ischaemic lesions as defined by an invasive FFR $\leq$ 0.80 or by decreased quantitative myocardial blood flow (47-51). The number of adverse plaque features appear to increase as stenosis severity increase, but the presence of high-risk plaque also remains an independent predictor of ischaemia regardless of stenosis severity, particularly positive remodelling (47, 48, 51). The mechanisms for these findings are not clear but reflect the complex relationship between coronary atherosclerosis and ischemia. Positive remodelling and the lipid-rich necrotic core of the vulnerable plaque may predispose to local endothelial dysfunction and altered shear stress, thus altering impairing arterial vasomotor function. This hypothesis is supported by a recent exploratory study in which high-risk plaque characteristics were more strongly related to invasive pressure measurements during hyperaemia than during rest (52). The adaptive arterial remodelling response to the progression of atheroma – the Glagov phenomenon – may also reach its limit with a certain volume of plaque, at which point luminal encroachment, obstruction to flow and ischaemia may rapidly progress (53).

PET provides the gold standard non-invasive assessment of myocardial perfusion. Unlike FFR, PET is able to provide a quantitative assessment of absolute hyperaemic blood flow and myocardial blood flow reserve, thus integrating the combined effect of epicardial coronary arterial atherosclerosis as well as microvascular disease. The Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography (PACIFIC) study demonstrated PET to be superior to CTCA and single-photon emission computed tomography (SPECT) for the diagnosis of ischaemia (based on invasive FFR) (54). Although this study showed only limited additional diagnostic value with hybrid imaging, a recent meta-analysis confirmed incremental diagnostic performance with hybrid anatomy/perfusion imaging compared to CTCA (55). Additionally, several retrospective studies consistently described an incremental prognostic value of combining myocardial perfusion imaging and CTCA (56, 57). Further data is now needed to investigate the association between adverse plaque features and myocardial perfusion on PET, to assess whether the latter might also provide a surrogate for unstable coronary plaque phenotypes.

The future of non-invasive coronary anatomy/physiology imaging is therefore extremely promising; there is great appeal in deriving a hybrid dataset assessing coronary anatomy, plaque morphology, plaque burden and coronary flow at both a lesion and vessel level. Randomized clinical trials will be highly anticipated.

CURRENT LIMITATIONS

Although the appeal of hybrid imaging is clear, there remain some limitations. Most crucially, until recently there has been a lack of randomised data demonstrating the ability of these imaging techniques to change outcomes. We now have this data supporting the use of CTCA, but there is a major need for similar data demonstrating the benefits of hybrid non-invasive ischaemia testing. Furthermore, access to scanners and integration of these imaging techniques into clinical workflows in imaging departments must be considered. Costs is also an issue, particularly with regards to the production of bespoke radiotracers for nuclear imaging. Consequently, which test to use in which patients in what setting must be carefully considered, taking into account all of these factors. This is in addition to other clinical factors that may influence the choice of test, such as patient age, likelihood of calcific disease, ability to achieve adequate heart rate control, comorbidities and acceptable radiation dose.

CASE 1

A 57-year-old man with type 2 diabetes mellitus presented with a non-ST elevation myocardial infarction (NSTEMI) and underwent percutaneous coronary intervention with two drug-eluting stents to the proximal right coronary artery (RCA) and posterior left ventricular artery (PLV). Six months later, he re-presented with another NSTEMI despite appropriate preventative therapies. Invasive coronary angiography demonstrated severe in-stent restenosis in the proximal stent and a further severe de novo mid-RCA (Figure 1A). Optical coherence tomography demonstrated plaque rupture with red thrombus in the mid-vessel lesion and aggressive neointimal hyperplasia in the proximal lesion (Figure 1B-C). Two drug-eluting stents were implanted with a good angiographic result (Figure 1D). The left system, particularly the left anterior descending artery (LAD), had diffuse plaque without obstructive disease (Figure 1E). As part of a research study, the patient underwent 18F-NaF PET-CT six weeks later. This demonstrated three discrete regions of focal uptake in the proximal, mid and distal RCA (arrows). Although the mid-RCA lesion was the culprit, the highest uptake was in the proximal restenotic lesion. In contrast to the RCA, the diffusely diseased LAD had non-obstructive calcific plaque without high-risk features on CTCA and did not demonstrate any 18F-NaF uptake (Figure 1F).

CASE 2

A patient was referred three weeks after an episode of chest pain with a late presentation myocardial infarction. He was not revascularized due to established infarction. Six months post-infarct, he underwent 18F-NaF PET-MR. Whole-heart, 3-dimensional, contrast-enhanced coronary MR angiography using a respiratory-navigated, electrocardiographically triggered, inversion-recovery fast spoiled gradient-echo sequence demonstrated a severe culprit plaque in the proximal LAD (Figure 1A). Extensive near-transmural infarction in this territory was seen on late gadolinium enhancement (Figure 1B). Focal 18F-NaF uptake was noted in the culprit lesion (Figure 1C-D, white arrowheads) as well as in the aorta and mitral annulus (black arrows). Adapted from Robson *et al* (41).

CONCLUSIONS

The field of cardiovascular atherosclerosis imaging is burgeoning, with increasing availability and uptake of CT and CMR in particular. Hybrid imaging platforms combine these modalities with PET, which together provide detailed information about coronary anatomy, flow, plaque morphology and disease activity, potentially expanding our pathophysiological understanding of atherosclerosis and improving risk stratification. Further studies are now required to investigate the clinical utility of this approach and determine whether hybrid imaging of the vulnerable plaque can improve patient outcomes.

ACCEPTED MANUSCRIPT

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REFERENCES

1. GBD Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.

2. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. J Am Coll Cardiol. 2006;47(8 Suppl):C13-8.

3. Arbab-Zadeh A, Fuster V. The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. J Am Coll Cardiol. 2015;65(8):846-55.

4. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226-35.

5. Chang HJ, Lin FY, Lee SE, Andreini D, Bax J, Cademartiri F, et al. Coronary Atherosclerotic Precursors of Acute Coronary Syndromes. J Am Coll Cardiol. 2018;71(22):2511-22.

6. Waksman R, editor Assessment of Coronary Near-Infrared Spectroscopy Imaging to Detect Vulnerable Plaques and Vulnerable Patients; The Lipid-Rich Plaque Study. Transcatheter Cardiovascular Therapeutics; 2018 24/9/2018; San Diego, California.

7. Tanaka A, Shimada K, Yoshida K, Jissyo S, Tanaka H, Sakamoto M, et al. Non-invasive assessment of plaque rupture by 64-slice multidetector computed tomography--comparison with intravascular ultrasound. Circulation journal : official journal of the Japanese Circulation Society. 2008;72(8):1276-81.

8. Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, et al. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. JACC Cardiovascular imaging. 2009;2(12):1412-9.

9. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol. 2007;50(4):319-26.

10. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, et al. Plaque Characterization by Coronary Computed Tomography Angiography and the Likelihood of Acute Coronary Events in Mid-Term Follow-Up. J Am Coll Cardiol. 2015;66(4):337-46.

11. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed Tomographic Angiography Characteristics of Atherosclerotic Plaques Subsequently Resulting in Acute Coronary Syndrome. Journal of the American College of Cardiology. 2009;54(1):49-57.

12. Yamamoto H, Kihara Y, Kitagawa T, Ohashi N, Kunita E, Iwanaga Y, et al. Coronary plaque characteristics in computed tomography and 2-year outcomes: The PREDICT study. Journal of cardiovascular computed tomography. 2018;12(5):436-43.

13. Ferencik M, Mayrhofer T, Bittner DO, Emami H, Puchner SB, Lu MT, et al. Use of High-Risk Coronary Atherosclerotic Plaque Detection for Risk Stratification of Patients With Stable Chest Pain: A Secondary Analysis of the PROMISE Randomized Clinical Trial. JAMA Cardiol. 2018;3(2):144-52.

14. Williams M, Moss A, Dweck M, Adamson P, Alam S, Hunter A, et al. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. Journal of the American College of Cardiology. 2019;73(3. In press.).

15. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. Journal of the American College of Cardiology. 2014;64(7):684-92.

16. Kawasaki T, Koga S, Koga N, Noguchi T, Tanaka H, Koga H, et al. Characterization of hyperintense plaque with noncontrast T(1)-weighted cardiac magnetic resonance coronary plaque imaging: comparison with multislice computed tomography and intravascular ultrasound. JACC Cardiovascular imaging. 2009;2(6):720-8.

17. Matsumoto K, Ehara S, Hasegawa T, Sakaguchi M, Otsuka K, Yoshikawa J, et al. Localization of Coronary High-Intensity Signals on T1-Weighted MR Imaging: Relation to Plaque Morphology and Clinical Severity of Angina Pectoris. JACC Cardiovascular imaging. 2015;8(10):1143-52.

18. Noguchi T, Tanaka A, Kawasaki T, Goto Y, Morita Y, Asaumi Y, et al. Effect of Intensive Statin Therapy on Coronary High-Intensity Plaques Detected by Noncontrast T1-Weighted Imaging: The AQUAMARINE Pilot Study. Journal of the American College of Cardiology. 2015;66(3):245-56.

19. Oshita A, Kawakami H, Miyoshi T, Seike F, Matsuoka H. Characterization of high-intensity plaques on noncontrast T1-weighted magnetic resonance imaging by coronary angioscopy. Journal of cardiology. 2017;70(6):520-3.

20. Matsumoto K, Ehara S, Hasegawa T, Nishimura S, Shimada K. The signal intensity of coronary culprit lesions on T1-weighted magnetic resonance imaging is directly correlated with the accumulation of vulnerable morphologies. International journal of cardiology. 2017;231:284-6.

21. Woodside DG, Tanifum EA, Ghaghada KB, Biediger RJ, Caivano AR, Starosolski ZA, et al. Magnetic Resonance Imaging of Atherosclerotic Plaque at Clinically Relevant Field Strengths (1T) by Targeting the Integrin alpha4beta1. Scientific reports. 2018;8(1):3733.

22. Xie Y, Kim YJ, Pang J, Kim JS, Yang Q, Wei J, et al. Coronary Atherosclerosis T1-Weighed Characterization With Integrated Anatomical Reference: Comparison With High-Risk Plaque Features Detected by Invasive Coronary Imaging. JACC Cardiovascular imaging. 2017;10(6):637-48.

23. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, et al. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. Circulation. 2002;105(23):2708-11.

24. Silvera SS, Aidi HE, Rudd JH, Mani V, Yang L, Farkouh M, et al. Multimodality imaging of atherosclerotic plaque activity and composition using FDG-PET/CT and MRI in carotid and femoral arteries. Atherosclerosis. 2009;207(1):139-43.

25. Tarkin JM, Joshi FR, Rudd JH. PET imaging of inflammation in atherosclerosis. Nature reviews Cardiology. 2014;11(8):443-57.

26. Joshi NV, Toor I, Shah AS, Carruthers K, Vesey AT, Alam SR, et al. Systemic Atherosclerotic Inflammation Following Acute Myocardial Infarction: Myocardial Infarction Begets Myocardial Infarction. Journal of the American Heart Association. 2015;4(9):e001956.

27. Wykrzykowska J, Lehman S, Williams G, Parker JA, Palmer MR, Varkey S, et al. Imaging of inflamed and vulnerable plaque in coronary arteries with 18F-FDG PET/CT in patients with suppression of myocardial uptake using a low-carbohydrate, high-fat preparation. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2009;50(4):563-8.

28. Rogers IS, Nasir K, Figueroa AL, Cury RC, Hoffmann U, Vermylen DA, et al. Feasibility of FDG Imaging of the Coronary Arteries: Comparison Between Acute Coronary Syndrome and Stable Angina. JACC: Cardiovascular Imaging. 2010;3(4):388-97.

29. Joshi NV, Vesey AT, Williams MC, Shah AS, Calvert PA, Craighead FH, et al. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. Lancet. 2014;383(9918):705-13.

30. Creager MD, Hohl T, Hutcheson JD, Moss AJ, Schlotter F, Blaser MC, et al. (18)F-Fluoride Signal Amplification Identifies Microcalcifications Associated With Atherosclerotic Plaque Instability in Positron Emission Tomography/Computed Tomography Images. Circ Cardiovasc Imaging. 2019;12(1):e007835.

31. Hutcheson JD, Maldonado N, Aikawa E. Small entities with large impact: microcalcifications and atherosclerotic plaque vulnerability. Current opinion in lipidology. 2014;25(5):327-32.

32. Derlin T, Richter U, Bannas P, Begemann P, Buchert R, Mester J, et al. Feasibility of 18F-sodium fluoride PET/CT for imaging of atherosclerotic plaque. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2010;51(6):862-5.

33. Dweck MR, Chow MW, Joshi NV, Williams MC, Jones C, Fletcher AM, et al. Coronary arterial 18F-sodium fluoride uptake: a novel marker of plaque biology. J Am Coll Cardiol. 2012;59(17):1539-48.

34. Irkle A, Vesey AT, Lewis DY, Skepper JN, Bird JL, Dweck MR, et al. Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. Nature communications. 2015;6:7495.

35. Marchesseau S, Seneviratna A, Sjoholm AT, Qin DL, Ho JXM, Hausenloy DJ, et al. Hybrid PET/CT and PET/MRI imaging of vulnerable coronary plaque and myocardial scar tissue in acute myocardial infarction. J Nucl Cardiol. 2017;10.1007/s12350-017-0918-8.

36. Kitagawa T, Yamamoto H, Nakamoto Y, Sasaki K, Toshimitsu S, Tatsugami F, et al. Predictive Value of (18)F-Sodium Fluoride Positron Emission Tomography in Detecting High-Risk Coronary Artery Disease in Combination With Computed Tomography. Journal of the American Heart Association. 2018;7(20):e010224.

37. Rubeaux M, Joshi NV, Dweck MR, Fletcher A, Motwani M, Thomson LE, et al. Motion Correction of 18F-NaF PET for Imaging Coronary Atherosclerotic Plaques. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2016;57(1):54-9.

38. Doris MK, Otaki Y, Krishnan SK, Kwiecinski J, Rubeaux M, Alessio A, et al. Optimization of reconstruction and quantification of motion-corrected coronary PET-CT. J Nucl Cardiol. 2018;10.1007/s12350-018-1317-5.

39. Lassen ML, Kwiecinski J, Cadet S, Dey D, Wang C, Dweck MR, et al. Data-driven gross patient motion detection and compensation: Implications for coronary (18)F-NaF PET imaging. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018;10.2967/jnumed.118.217877.

40. Kwiecinski J, Adamson PD, Lassen ML, Doris MK, Moss AJ, Cadet S, et al. Feasibility of Coronary (18)F-Sodium Fluoride Positron-Emission Tomography Assessment With the Utilization of Previously Acquired Computed Tomography Angiography. Circ Cardiovasc Imaging. 2018;11(12):e008325.

41. Robson PM, Dweck MR, Trivieri MG, Abgral R, Karakatsanis NA, Contreras J, et al. Coronary Artery PET/MR Imaging: Feasibility, Limitations, and Solutions. JACC Cardiovascular imaging. 2017;10(10 Pt A):1103-12.

42. Andrews JPM, Fayad ZA, Dweck MR. New methods to image unstable atherosclerotic plaques. Atherosclerosis. 2018;272:118-28.

43. Tarkin JM, Joshi FR, Evans NR, Chowdhury MM, Figg NL, Shah AV, et al. Detection of Atherosclerotic Inflammation by (68)Ga-DOTATATE PET Compared to [(18)F]FDG PET Imaging. J Am Coll Cardiol. 2017;69(14):1774-91.

44. Gaemperli O, Shalhoub J, Owen DR, Lamare F, Johansson S, Fouladi N, et al. Imaging intraplaque inflammation in carotid atherosclerosis with 11C-PK11195 positron emission tomography/computed tomography. Eur Heart J. 2012;33(15):1902-10.

45. Derlin T, Sedding DG, Dutzmann J, Haghikia A, König T, Napp LC, et al. Imaging of chemokine receptor CXCR4 expression in culprit and nonculprit coronary atherosclerotic plaque using motion-corrected [68Ga]pentixafor PET/CT. European journal of nuclear medicine and molecular imaging. 2018;45(11):1934-44.

46. Lee JM, Choi G, Koo BK, Hwang D, Park J, Zhang J, et al. Identification of High-Risk Plaques Destined to Cause Acute Coronary Syndrome Using Coronary Computed Tomographic Angiography and Computational Fluid Dynamics. JACC Cardiovascular imaging. 2018;10.1016/j.jcmg.2018.01.023.

47. Park H-B, Heo R, ó Hartaigh B, Cho I, Gransar H, Nakazato R, et al. Atherosclerotic Plaque Characteristics by CT Angiography Identify Coronary Lesions That Cause Ischemia: A Direct Comparison to Fractional Flow Reserve. JACC: Cardiovascular Imaging. 2015;8(1):1-10.

48. Nakazato R, Park H-B, Gransar H, Leipsic JA, Budoff MJ, Mancini GBJ, et al. Additive diagnostic value of atherosclerotic plaque characteristics to non-invasive FFR for identification of lesions causing ischaemia: results from a prospective international multicentre trial. EuroIntervention. 2016;12(4):473-81.

49. Gaur S, Øvrehus KA, Dey D, Leipsic J, Bøtker HE, Jensen JM, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. European Heart Journal. 2016;37(15):1220-7.

50. Ovrehus KA, Gaur S, Leipsic J, Jensen JM, Dey D, Botker HE, et al. CT-based total vessel plaque analyses improves prediction of hemodynamic significance lesions as assessed by fractional flow reserve in patients with stable angina pectoris. Journal of cardiovascular computed tomography. 2018;12(4):344-9.

51. Driessen RS, Stuijfzand WJ, Raijmakers PG, Danad I, Min JK, Leipsic JA, et al. Effect of Plaque Burden and Morphology on Myocardial Blood Flow and Fractional Flow Reserve. J Am Coll Cardiol. 2018;71(5):499-509.

52. Driessen RS, Stuijfzand WJ, Raijmakers PG, Danad I, Min JK, Leipsic JA, et al. Vulnerable plaques are revealed by fractional flow reserve but not by instantaneous wave-free ratio. European Heart Journal. 2018;39(suppl_1).

53. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol. 2013;61(10):1041-51.

54. Danad I, Raijmakers PG, Driessen RS, Leipsic J, Raju R, Naoum C, et al. Comparison of Coronary CT Angiography, SPECT, PET, and Hybrid Imaging for

Diagnosis of Ischemic Heart Disease Determined by Fractional Flow Reserve. JAMA Cardiol. 2017;2(10):1100-7.

55. Rizvi A, Han D, Danad I, B OH, Lee JH, Gransar H, et al. Diagnostic Performance of Hybrid Cardiac Imaging Methods for Assessment of Obstructive Coronary Artery Disease Compared With Stand-Alone Coronary Computed Tomography Angiography: A Meta-Analysis. JACC Cardiovascular imaging. 2018;11(4):589-99.

56. Pazhenkottil AP, Benz DC, Gräni C, Madsen MA, Mikulicic F, von Felten E, et al. Hybrid SPECT Perfusion Imaging and Coronary CT Angiography: Long-term Prognostic Value for Cardiovascular Outcomes. Radiology. 2018;288(3):694-702.

57. Maaniitty T, Stenstrom I, Bax JJ, Uusitalo V, Ukkonen H, Kajander S, et al. Prognostic Value of Coronary CT Angiography With Selective PET Perfusion Imaging in Coronary Artery Disease. JACC Cardiovascular imaging. 2017;10(11):1361-70.

FIGURE LEGENDS

Figure 1

Invasive angiography (A, D, E), optical coherence tomography (B, C) and positron emission tomography-computed tomography (F, G) for Case 1. Descriptions provided in case vignette.

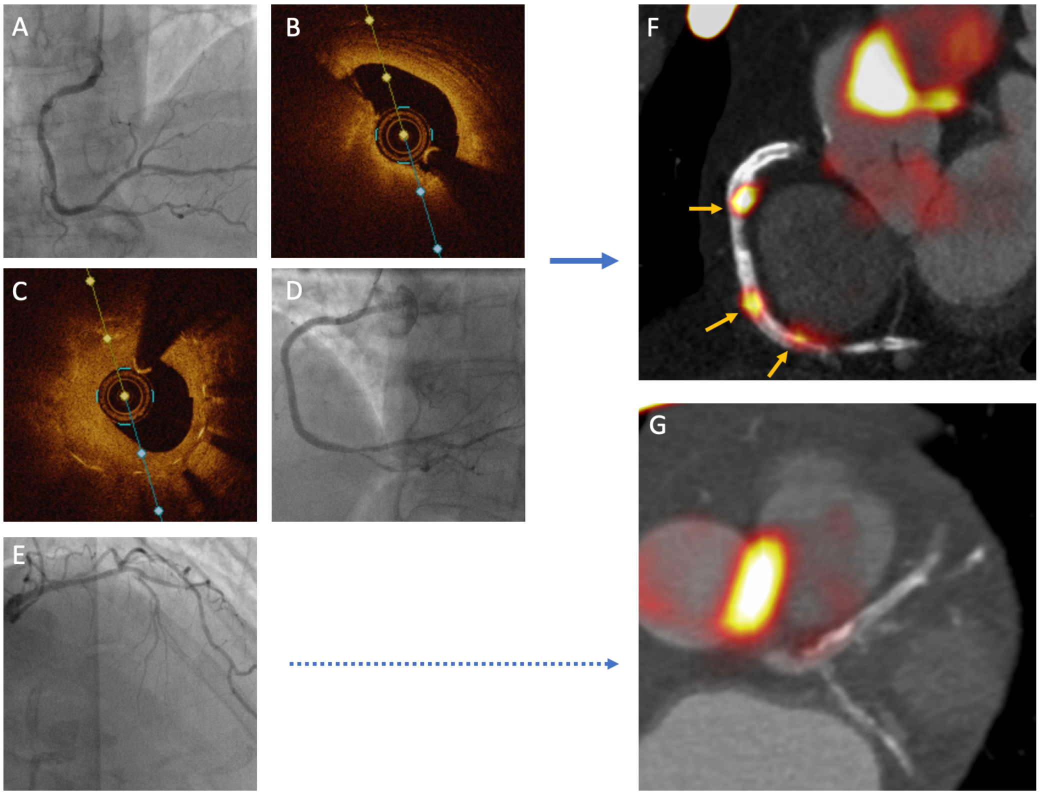
Figure 2

Cardiac magnetic resonance for Case 2. Descriptions provided in case vignette.

Table 1 Positron emission tomography radiotracers targeting vulnerable plaque

Target	Ligand	Radiotracer	Current applications in atherosclerosis
Macrophage activation	Glucose transporter protein system. Conversion to 18F-FDG-6-phosphate and intracellular accumulation	^{18}F-FDG	Prospective *in vivo* studies in extracardiac atherosclerosis. Correlation with atherosclerosis and cardiovascular risk. Myocardial signal spill-over limits coronary artery assessment (35, 37).
	Somatostatin receptor subtype 2	^{68}Ga-DOTATATE	Prospective *in vivo* studies in cardiac and extracardiac atherosclerosis. Correlation with culprit coronary lesions and high-risk features on CTCA (52).
	Translocator protein 18-kDa	^{11}C-PK11195	Prospective *in vivo* study in carotid atherosclerosis (67). Short half-life and variable metabolism.
	Choline kinase phosphorylated to phosphatidylcholine	^{18}F-FCH	Retrospective *in vivo* study demonstrating correlation with large vessel atherosclerosis and an inverse relationship with calcification (68).
Apoptosis	Phosphatidylserine	Annexin V	Prospective *in vivo* pilot data in carotid atherosclerosis (69).
Hypoxia	Reduction to amine derivative in low oxygen environment	^{18}F-FMISO	Prospective *in vivo* pilot data in carotid atherosclerosis (70).
	Reduction to amine derivative in low O_2 environment	^{18}F-HX4	Prospective *in vivo* pilot data in carotid atherosclerosis (71).
Microcalcification	Hydroxyapatite	^{18}F-NaF	Prospective *in vivo* studies in coronary and extracardiac atherosclerosis. Correlation with culprit coronary lesions and high-risk features on CTCA (37, 41, 44, 72).
Angiogenesis	αVβ3 & αVβ5 integrin	^{18}F-Fluciclatide	Prospective *in vivo* pilot data in the aorta (73).
	αVβ3 integrin	^{18}F-RGD-K5	*Ex vivo* study in carotid atherosclerosis (74).
Thrombus	Glycoprotein IIb/IIIa platelet receptor	^{18}F-GP1	Prospective *in vivo* pilot data in arterial thromboembolic disease (75).

18F-FDG: 18-fluorodeoxyglucose, CTCA: computed tomography coronary angiography, 18F-FCH: 18F-fluorocholine, 18F-FMISO: 18F-fluoromisonidazole, 18F-HX4: 18F-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol, 18F-NaF: 18F-sodium fluoride, 18F-RGD-K5: arginine-glycine-aspartate-K5.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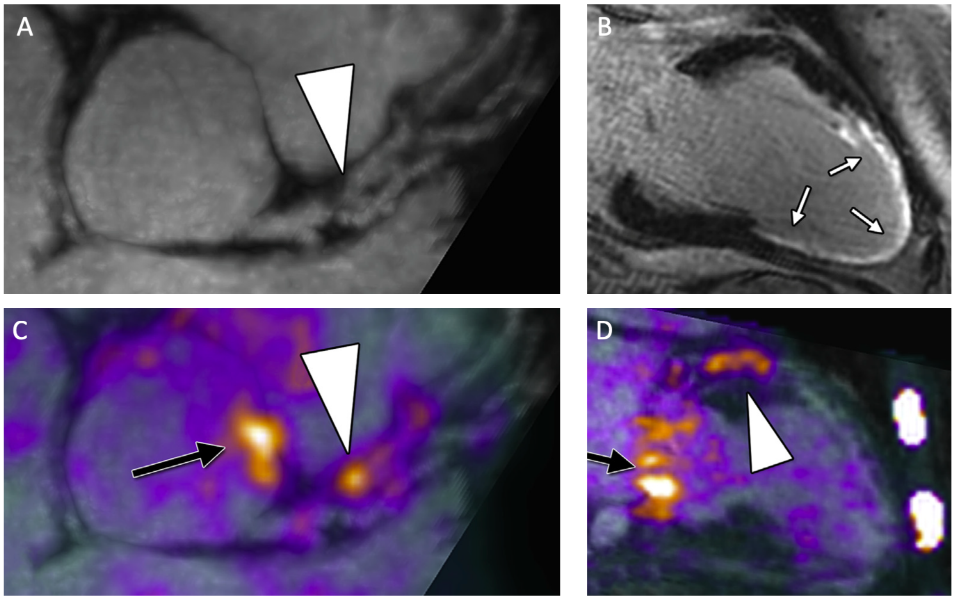
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